ORIGINAL RESEARCH

Comparative Safety Assessment of High and Low Doses of Anlotinib in Combination with PD-1 Monoclonal Antibody for Advanced Non-small Cell Lung Cancer Patients

Lin Wan, MD; Yan Xu, MM; Liqiong Liu, MM; Hui Huang, MD

ABSTRACT

Background • The advent of immunotherapy has revolutionized non-small cell lung cancer (NSCLC) treatment. Anlotinib (AN), a multitargeted tyrosine kinase inhibitor, holds promise in combination with PD-1 monoclonal antibody therapy. Understanding the impact of optimal dosage is pivotal.

Objective • This study aims to assess the comparative efficacy of high-dose AN versus low-dose AN when combined with PD-1 monoclonal antibody for the treatment of NSCLC.

Methods • A total of 70 patients with NSCLC undergoing PD-1 monoclonal antibody therapy at our hospital from June 2020 to January 2022 were selected. The low-dose group (n=33) received AN at 8 mg and 10 mg. In comparison, the high-dose group (n=37) received AN at 12 mg. Comparative analyses included assessment of clinical efficacy, adverse reactions, prognosis, survival, changes in T lymphocyte subsets, inflammatory factors pre and post-chemotherapy, and treatment satisfaction.

Results • No significant difference was observed in clinical efficacy and prognosis between the two groups ($P > .05$). The low-dose group exhibited fewer adverse reactions and inflammatory responses, along with improved immune function post-treatment ($P < .05$). Treatment satisfaction was higher in the low-dose group compared to the high-dose group ($P < .05$).

Conclusions • Findings suggest that combining low-dose AN with PD-1 monoclonal antibody therapy is a safer approach in the treatment of advanced NSCLC. These findings advocate for the adoption of a tailored, lower-dose AN regimen, presenting a clinically sound and patient-centered strategy in the ongoing pursuit of optimized treatment modalities for advanced NSCLC. (*Altern Ther Health Med.* [E-pub ahead of print.])

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INTRODUCTION

Lung cancer (LC) ranks among the most prevalent malignant tumors, with non-small cell lung cancer (NSCLC) constituting approximately 85% of all LC cases.[1] According to the World Health Organization (WHO) statistics, the global incidence of new NSCLC cases surpassed 500 000 in 2021, revealing a concerning trend toward a younger age demographic among patients.[2,3] Research indicates that NSCLC is intricately linked to prolonged interactions between environmental factors and genes.[3]

Due to the absence of typical symptoms in early-stage patients, most diagnoses occur during the intermediate or advanced stages, marked by fatigue, weight loss, decreased appetite, and local symptoms like dyspnea, cough, and hemoptysis.[4] Unfortunately, NSCLC is characterized by a low 5-year survival rate.[4] Traditional treatments encompass radiotherapy, chemotherapy, and targeted therapy.[5,6] In the evolving landscape of medical technology, immunotherapy emerges as a novel treatment modality, gaining traction in clinical practice.

The PD-1 monoclonal antibody stands as the most extensively researched and promptly implemented immunotherapy in current medical practice.[7] However, clinical observations reveal its limited efficacy and pronounced side effects in monotherapy.[8] Consequently, a strategic shift towards combined therapy, integrating multiple drugs or approaches, has gained prominence.

Anlotinib (AN), recognized as a multitargeted tyrosine kinase inhibitor, not only impedes tumor angiogenesis but also serves as a targeted drug responsive to combination with chemotherapy.[9] AN exhibits excellent tolerability, rendering it suitable for a broad spectrum of populations, and has become a standard in the treatment of advanced LC.[10]

However, the standalone anti-tumor efficacy of AN demonstrates a positive correlation with the dosage, sparking debates about the influence of dose on the augmented effectiveness of PD-1 monoclonal antibody in combination.[11]

Therefore, there is a necessity to compare the safety profiles of high and low doses of AN when combined with PD-1 monoclonal antibody in the treatment of advanced NSCLC patients. This study focuses on such comparison, aiming to furnish valuable insights and guidance for future clinical treatment approaches.

MATERIALS AND METHODS

Study Design

A cohort of 70 patients diagnosed with advanced NSCLC, having undergone at least first-line treatment at our hospital between June 2020 and January 2022, constituted the study participants. They were stratified into two groups based on the AN dosage: a low-dose group (8 mg and 10 mg) comprising 33 patients and a high-dose group (12 mg) comprising 37 patients. The Ethics Committee granted ethical approval for this study, and all study procedures adhered strictly to the principles outlined in the *Declaration of Helsinki*.

Inclusion and Exclusion Criteria

Inclusion criteria were as follows: (1) Patients diagnosed with NSCLC confirmed through pathological examination and clinically staged as stage IV;[12] (2) individuals with comprehensive medical records and follow-up data; (3) those who experienced first-line treatment failure; (4) individuals with complete medical documentation available for follow-up; (5) participants who, along with their families, were informed about the study and provided consent. Exclusion criteria were as follows: (1) Patients with complications such as heart, liver, kidney, thyroid, bone marrow, or other organ dysfunction; (2) individuals with concurrent autoimmune diseases; (3) those experiencing major organ failure; and (4) patients in the pregnancy or lactating period.

Treatment Method

Treatment Regimen. Patients received oral administration of Anlotinib AN from Zhengda Tianqing Pharmaceutical Group Co., Ltd (H20180003) at doses of 8, 10, and 12 mg/kg, guided by the physician's dosage recommendations, with a one-week pause following every two weeks of use.

Dosage Considerations. The administration dosage and schedule of PD-1 monoclonal antibody varied, encompassing pembrolizumab (Keytruda) at 2 mg/kg, nivolumab (Opdivo) at 3 mg/kg, sintilimab (Tyvyt) at 3 mg/kg, toripalimab (Tuoyi) at 3 mg/kg, and tislelizumab (Baizean) at 200 mg per administration. Pembrolizumab, sintilimab, and tislelizumab were administered every 21 days per cycle, while toripalimab and nivolumab were given every 14 days per cycle.

Treatment Cycle Initiation. Prior to each treatment cycle, comprehensive hematology tests and electrocardiograms (ECGs) were mandatory. The initiation of each anti-tumor treatment cycle was contingent upon the absence of any noticeable abnormalities in these pre-cycle assessments.

T Lymphocyte Subset Analysis

Venous blood was drawn from patients one day before treatment initiation and after completion of two treatment cycles. The alterations in peripheral blood T lymphocyte subsets, specifically the percentages of CD3+, CD4+, and CD8+ cells, were assessed using flow cytometry (Beckman Coulter, CytoFLEX LX flow cytometer). Additionally, the CD4+/CD8+ ratio was calculated to provide a comprehensive insight into the immune profile changes during the treatment course.

Inflammatory Factor Assessment

Hypersensitive C-reactive protein (hs-CRP) levels were assessed using an automated hematology analyzer (Myriad, BC-3200 blood cell analyzer), while interleukin-1β (IL-1β) and tumor necrosis factor-α (TNF-α) were measured through enzyme-linked immunosorbent assay (ELISA). The assay kits, sourced from Shanghai Xuanya Biotechnology Co., Ltd., were employed, and all procedures adhered rigorously to the instructions provided with the kits.

Clinical Efficacy Assessment

Following two treatment cycles, patient evaluation for clinical efficacy adhered to the Response Evaluation Criteria in Solid Tumors (RECIST),[13] characterized by the criteria outlined below: (1) Complete Response (CR): Disappearance of all target lesions; (2) Partial Response (PR): A minimum 30% decrease in the sum of the longest diameters (LD) of target lesions; (3) Progressive Disease (PD): A minimum 20% increase in the sum of the LD of target lesions, with an absolute increase of at least 5 mm. The emergence of one or more new lesions is also considered progression; (4) Stable Disease (SD): Neither significant shrinkage qualifying for PR nor notable increase qualifying for PD. (5) Objective Response Rate (ORR): Calculated as (PR + CR) / Total number × 100%; (6) Disease Control Rate (DCR): Calculated as (PR + CR + SD) / Total number × 100%.

Adverse Reaction Assessment

Adverse reactions were systematically assessed through pre-treatment cycles, utilizing hematology, biochemistry, thyroid function, ECG, and myocardial enzyme tests. The evaluation process adhered to the guidelines outlined in the Common Terminology Criteria for Adverse Events (CTCAE).[14]

Treatment Satisfaction Survey

After the completion of chemotherapy, a survey was conducted to assess the treatment satisfaction of patients in both groups. An anonymous questionnaire was employed for this purpose, with response options categorized as 'very satisfied,' 'basic satisfaction,' and 'dissatisfaction.' The overall satisfaction rate was calculated as Total Satisfaction = (Very Satisfied + Basic Satisfaction) / Total × 100%.

Prognosis

The study conducted a statistical analysis of the progression-free survival (PFS), defined as the time from the initiation of treatment to documented disease progression or death from any cause, for patients in both groups. Additionally, the overall survival (OS), calculated as the time from the commencement of AN combined with PD-1 monoclonal antibody therapy to death or last follow-up, was thoroughly examined.

Outcome Measures

A comprehensive statistical analysis was conducted to assess various outcome measures in both patient groups. It included: (1) Clinical efficacy: we evaluated the effectiveness of the treatment; (2) Adverse reactions: we analyzed any untoward responses to the treatment; (3) Treatment satisfaction: we assessed the patient contentment post-chemotherapy; (4) Prognosis and survival: we examined the progression-free survival, overall survival, and disease prognosis; (5) Immunological changes: we compared alterations in T lymphocyte subsets and inflammatory factors before treatment initiation.

Statistical Analysis

The statistical analysis for this study was executed using SPSS 24.0 software (IBM). Gender and clinical efficacy data, presented as counts and percentages, underwent comparison through the chi-square (χ^2) test. Age and T lymphocyte subsets, expressed as mean ± standard deviation ($\bar{x} \pm s$), were subjected to analysis using the independent samples t test for between-group comparisons and the paired t test for within-group comparisons. The survival rate was determined using the Kaplan-Meier method, and comparisons were made using the Log-rank test. A significance level of $P < .05$ was established to denote statistical significance.

RESULTS

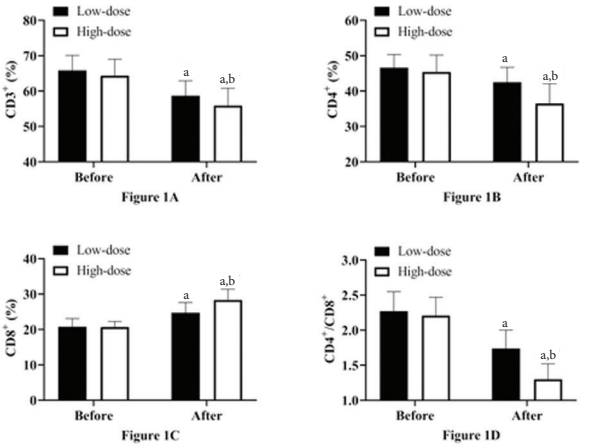
Comparison of Clinical Baseline Data Between Groups

No statistically significant differences were observed in age, gender, and other demographic data between the two groups ($P > .05$), affirming their comparability, see Table 1. This finding suggests that the initial clinical characteristics of the study cohorts were similar, enhancing the validity of subsequent comparative analyses.

Table 1. Comparison of Baseline data between the groups

Group	n	Male *vs.* Female	Age	Long-Term Smoking Yes *vs.* No	Family History of LC Yes *vs.* No
Low Dose	33	27 (81.82) *vs.* 6 (18.18)	65.79±4.90	20 (60.61) *vs.* 13 (39.39)	3 (9.09) *vs.* 30 (90.91)
High Dose	37	28 (75.68) *vs.* 9 (24.32)	66.08±4.87	24 (64.86) *vs.* 13 (35.14)	5 (13.51) *vs.* 32 (86.49)
χ^2 and t		0.391	0.251	0.136	0.337
P value		.532	.803	.713	.562

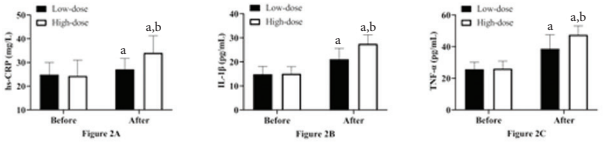
Figure 1. Comparison of T Lymphocyte Subsets before and after Treatment. (A): CD3+; (B): CD4+; (C): CD8+; (D): CD4+/CD8+



[a]$P < .05$ vs. Before Treatment
[b]$P < .05$ vs. Low-dose Group

Note: The figure illustrates the changes in T lymphocyte subsets (CD3+, CD4+, CD8+, and CD4+/CD8+) before and after treatment.

Figure 2. Comparison of Inflammatory Factors before and after Treatment. (A): hs-CRP; (B): IL-1β; (C): TNF-α.



[a]$P < .05$ vs. Before Treatment
[b]$P < .05$ vs. Low-dose Group

Note: The figure presents the variations in inflammatory factors (hs-CRP, IL-1β, and TNF-α) before and after treatment.

Comparison of Immune Function Between the Group Post-Treatment

Before treatment, there was no statistically significant difference in T lymphocyte subset results between the two groups ($P > .05$). However, post-treatment, the low-dose group exhibited higher levels of CD3+, CD4+, and CD4+/CD8+ and lower levels of CD8+ compared to the high-dose group ($P < .05$). Intra-group comparisons revealed that post-treatment, both groups experienced a decrease in CD3+, CD4+, and CD4+/CD8+ levels and an increase in CD8+ levels ($P < .05$), see Figure 1. These findings suggest an enhancement in immune function, particularly in the low-dose group, following the prescribed treatment.

Comparison of Inflammatory Reactions Between the Group Post-Treatment

There were no evident differences in the pre-treatment results of inflammatory factors between the two groups ($P > .05$). Post-treatment, there was a general elevation in all inflammatory factors. Intra-group comparisons revealed that hs-CRP), IL-1β, and TNF-α levels in the low-dose group were significantly lower than those in the high-dose group ($P < .05$), refer to Figure 2. These results suggest a notable reduction in inflammatory reactions, particularly in the low-dose group, following the treatment protocol.

Table 2. Comparison of Clinical Efficacy

Group	n	CR	PR	SD	PD	DCR	ORR
Low-dose	33	0 (0.0)	12 (36.36)	14 (42.42)	7 (21.21)	78.79	36.36
High-dose	37	0 (0.0)	15 (40.54)	14 (37.84)	8 (21.62)	78.38	40.54
χ^2						0.128	0.002
P value						0.720	0.967

Abbreviations: CR, Complete Response, PR, Partial Response, SD, Stable Disease, PD, Progressive Disease, DCR, Disease Control Rate, ORR, Objective Response Rate.

Table 3. Comparison of Adverse Reactions

Types	Level	Low-Dose (n=33)	High-Dose (n=37)	χ^2	*P* value
Nausea and Vomiting	1-2	11 (33.33)	6 (16.22)	6.293	.043
	3-4	5 (15.15)	15 (40.54)		
Hypertension	1-2	4 (12.12)	8 (21.62)	6.333	.042
	3-4	3 (9.09)	9 (24.32)		
Hand-Foot Syndrome	1-2	5 (15.15)	7 (18.92)	3.133	.209
	3-4	0 (0.0)	3 (8.11)		
Weakness	1-2	11 (33.33)	14 (37.84)	0.392	.822
	3-4	8 (24.24)	10 (27.03)		
Anemia	1-2	5 (15.15)	7 (18.92)	0.392	.822
	3-4	6 (18.18)	8 (21.62)		
Loss of Appetite	1-2	8 (24.24)	2 (5.41)	6.860	.032
	3-4	4 (12.12)	11 (29.73)		
Thrombocytopenia	1-2	4 (12.12)	2 (5.41)	2.119	.347
	3-4	3 (9.09)	7 (18.92)		

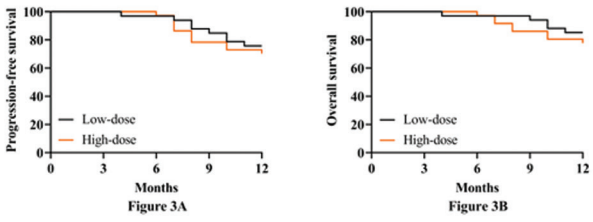
Note: The levels of adverse reactions are categorized as 1-2 (mild to moderate) and 3-4 (severe).

Table 4. Results Of the Treatment Satisfaction Survey

Group	n	Very Satisfied	Basically Satisfied	Dissatisfied	Total Satisfaction
Low-Dose	33	10 (30.30)	19 (57.58)	4 (12.12)	87.88
High-Dose	37	8 (21.62)	17 (45.95)	12 (32.43)	67.57
χ^2					4.081
P value					0.043

Note: The satisfaction levels are categorized as Very Satisfied, Basically Satisfied, and Dissatisfied. The Total Satisfaction is calculated as (Very Satisfied + Basically Satisfied)/Total × 100%.

Figure 3. Comparison of Prognosis. (A): PFS (Progression-Free Survival) (B): OS (Overall Survival)



Note: The figure depicts the comparison of prognosis, including PFS (Progression-Free Survival) in Figure 3A and OS (Overall Survival) in Figure 3B.

Comparison of Clinical Efficacy Between the Two Groups

Statistical analysis of clinical efficacy revealed no cases of CR in either group. The ORR was 36.36%, and the DCR was 78.79% in the low-dose group, while the high-dose group exhibited an ORR of 40.54% and a DCR of 78.38%. Importantly, no statistically significant differences were identified between the groups in either ORR or DCR ($P > .05$), refer to Table 2. This result indicates a similar clinical efficacy profile in both groups, supporting the notion that the treatment outcomes were comparable.

Comparison of Adverse Reactions Between the Groups

Throughout the treatment course, patients in both groups encountered adverse reactions, including nausea, vomiting, hypertension, hand-and-foot syndrome, and asthenia. Significant differences in the severity of asthenia and anemia between the two groups were not evident ($P > .05$). However, adverse reactions such as nausea, vomiting, and hypertension were significantly more pronounced in the low-dose group compared to the high-dose group ($P < .05$), refer to Table 3. These findings indicate a tendency towards milder adverse reactions in the high-dose group, emphasizing a potential benefit associated with the higher dosage.

Comparison of Treatment Satisfaction Between the Groups

The survey results revealed a notable disparity in treatment satisfaction, with the low-dose group reporting 87.88% satisfaction compared to 67.57% in the high-dose group, indicating a higher satisfaction level in the former ($P < .05$), see Table 4. This finding suggests that patients in the low-dose group expressed a more favorable perception of their treatment experience, underscoring the potential advantages associated with the lower-dosage regimen.

Prognosis Comparison Between the Two Groups

Follow-up outcomes indicated that the OS and PFS were (11.12±1.88) months and (11.53±1.50) months, respectively, in the low-dose group. In comparison, the high-dose group exhibited (10.86±2.00) months for OS and (11.24±1.71) months for PFS, with no statistically significant difference between the two groups ($P > .05$), refer to Figure 3. These findings suggest similar prognosis outcomes in both groups, reinforcing the notion that the choice of dosage did not significantly impact the overall and progression-free survival rates.

DISCUSSION

AN, as an anti-angiogenic drug, has demonstrated remarkable efficacy in halting the progression of NSCLC.[15] However, the determination of the optimal dosage remains elusive, particularly when used in combination with PD-1 monoclonal antibody. This study carefully compared the clinical effects of different AN dose in NSCLC treatment. The findings from this offer a more precise and insightful reference, providing valuable guidance for future NSCLC treatment strategies.

Within this study, both groups of patients exhibited a decrease in CD3+, CD4+, and CD4+/CD8+ levels and an increase in CD8+, hs-CRP, IL-1β, and TNF-α following treatment. These findings suggest a noticeable reduction in immune function and an increase of inflammatory reactions post AN combined with PD-1 monoclonal antibody chemotherapy. These phenomena could potentially be attributed to the toxic and side effects inherent in chemotherapy drugs. Importantly, these observed changes align consistently with the results obtained in previous pathological studies.[16,17]

The comparative results between the two groups revealed a more favorable immune function and a diminished inflammatory response in the low-dose group following treatment. These results suggest that the utilization of low-dose AN could be a more effective strategy in preserving patients' immune function and mitigating inflammatory responses. In our past investigation, we also observed that, in contrast to high-dose Apatinib, low-dose Apatinib demonstrated superior capabilities in normalizing tumor blood vessels.[18] Specifically, low-dose Apatinib exhibited a more pronounced inhibitory effect on myeloid suppressor cells and tumor-associated macrophages, further highlighting its potential advantages over high-dose counterparts.[18-19]

Anti-angiogenic drugs, exemplified by AN, primarily inhibit tumor growth and angiogenesis by targeting vascular endothelial growth factor receptors.[19] However, this process entails a significant inhibition of normal stem cell growth factors, fibroblast growth factors, platelet-derived growth factors, and others, contributing to the toxic and side effects associated with chemotherapeutic drugs.[20]

With an increase in the dose of AN, this inhibitory effect becomes more pronounced, detrimentally impacting patients' immune function and intensifying inflammatory reactions. We assume that this mechanism underlies the observed differences in the results of T lymphocyte subsets and inflammatory factors between the two groups in this study.

In the evaluation of patient clinical efficacy and prognosis, no significant differences were observed between the high-dose and low-dose groups. This finding indicates that the clinical treatment efficacy of low-dose AN is comparable to that of the high dose. The alteration of the tumor immune microenvironment by AN may explain this observation. Research indicates that AN inhibits the expression of PD-L1 in vascular endothelial cells, thereby disrupting the immune tolerance barrier, fostering CD8+ T cell infiltration, increasing the CD8+/fork-head box protein 3 (FoxP3+) ratio, and inducing changes in the tumor microenvironment.[21]

Furthermore, PD-1 monoclonal antibody has been demonstrated to promote vascular normalization,[22] allowing the optimization of the advantages of both drugs and generating a synergistic effect. Consequently, regardless of the AN dose, its synergistic potential with PD-1 monoclonal antibody can be utilized for anti-tumor benefits. The use of a lower dose of anti-angiogenic drugs in the low-dose group contributed to maintaining a more desirable overall health status, significantly enhancing the safety of the treatment. This assumption is further supported by the notably improved condition of the low-dose group in terms of adverse reactions compared to the control group within this study.

In this study the elevated treatment satisfaction in the low-dose group strongly indicates that the use of low-dose AN in combination with PD-1 monoclonal antibody results in an improved treatment experience. This positive outcome is likely associated with the milder adverse reactions and overall better physiological function observed in the low-dose group. Undoubtedly, these results ensure a superior clinical service for patients undergoing chemotherapy for advanced NSCLC in the future.

Study Limitations

However, several limitations in this study warrant improvement. Firstly, it is a small-sample retrospective analysis with a limited number of cases. Variations in tissue types and the gene mutation status of NSCLC may introduce variability in treatment outcomes, potentially influencing the final experimental results. Secondly, the follow-up time was short, increasing the likelihood of chance findings in prognosis analysis. Lastly, utilizing the same PD-1 monoclonal antibody across cases could enhance the accuracy of references for clinical use. In future, we aim to conduct a more comprehensive analysis to address these limitations.

CONCLUSION

In conclusion, our study underscores the comparable treatment effectiveness and patient outcomes achieved with both high and low doses of AN in conjunction with PD-1 monoclonal antibody for advanced NSCLC. However, the noteworthy findings reveal that the low-dose regimen not only maintains treatment efficacy but also enhances safety and preserves immune function. Consequently, advocating for the utilization of low-dose AN in tandem with PD-1 monoclonal antibody emerges as a prudent strategy, promising to elevate the overall quality of clinical medical services for advanced NSCLC in the future.

ETHICAL APPROVAL

Not applicable.

CONSENT TO PUBLISH

All authors gave final approval of the version to be published.

CONFLICTS OF INTEREST

The authors report no conflict of interest.

AVAILABILITY OF DATA AND MATERIALS

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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